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Dynamic cross-talk between microglia and peripheral monocytes underlies stress-induced neuroinflammation and behavioral consequences

Eric S. Wohleb *, Jean-Christophe Delpech

Department of Psychiatry, Yale University School of Medicine, USA

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ABSTRACT

Psychological stress promotes the development and recurrence of anxiety and depressive behavioral symptoms. Basic and clinical research indicates that stress exposure can influence the neurobiology of mental health disorders through dysregulation of neuroimmune systems. Consistent with this idea several studies show that repeated stress exposure causes microglia activation and recruitment of peripheral monocytes to the brain contributing to development of anxiety- and depressive-like behavior. Further studies show that stress-induced re-distribution of peripheral monocytes leads to stress-sensitized neuroimmune responses and recurrent anxiety-like behavior. These stress-associated immune changes are important because brain resident and peripheral immune cells contribute to physiological processes that support neuroplasticity. Thus, perturbations in neuroimmune function can lead to impaired neuronal responses and synaptic plasticity deficits that underlie behavioral symptoms of mental health disorders. In this review we discuss recent advances in neuroimmune regulation of behavior and summarize studies showing that stress-induced microglia activation and monocyte trafficking in the brain contribute to the neurobiology of mental health disorders.

Contents

1. Introduction

Mental health disorders, such as anxiety and depression, cause significant social and economic burden throughout the world. With the high prevalence of mental health disorders, such as major depression near 17%, it is imperative to better understand the pathophysiology leading to behavioral consequences (Kessler, 2003, Kessler et al., 2005, Murray et al., 2013). The neurobiology of mental health disorders is difficult to uncover as patients present heterogeneous symptoms and often experience remission and relapse. Despite these inconsistent features recent studies show that imbalances in glutamate and GABA (**γ-Aminobutyric acid**) may underlie behavioral symptoms of anxiety and depression (Kendell et al., 2005). Consistent with these hypotheses, clinical and preclinical studies indicate that anxiety and depressive symptoms are associated with deficits in neuroplasticity, specifically in the prefrontal cortex and hippocampus (Duman, 2009, Duric et al., 2012, Kang et al., 2012, Ota et al., 2014).

Exposure to psychosocial or environmental stressors is implicated in neuroplasticity deficits leading to anxiety- and depressive-like behaviors

* Corresponding author at: 34 Park Street, New Haven, CT 06510, USA.
E-mail address: eric.wohleb@yale.edu (E.S. Wohleb).

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(Christoffel et al., 2011, Popoli et al., 2012). This is consistent with clinical studies showing that psychological stress can lead to development and recurrence of depressive symptoms (Gilman et al., 2013, Kendler et al., 1999, McLaughlin et al., 2010). Coinciding with neurobiological changes, stress exposure influences the development, distribution, and activation of immune cells. Thus, stress-associated changes in immune function may drive the pathophysiology of mental health disorders. Indeed recent evidence indicates that resident and peripheral immune cells in the brain may drive the neurobiology of mental health disorders (Beumer et al., 2012, Hodes et al., 2015, Wohleb et al., 2015). This is plausible as preclinical studies demonstrate that neuroimmune components have an integral role in shaping neuronal responses and synaptic elements (Delpech et al., 2015). Here we will review primary neuroimmune components and how stress can lead to perturbations in neuroimmune function. Moreover, we will discuss how altered neuroimmune function may lead to neuroplasticity deficits implicated in mental health disorders.

2. Cellular neuroimmune components: in and outside the brain

The notion that the brain is an immune-privileged organ has evolved in recent decades as studies outline neuroimmune mechanisms that modulate physiological and pathological conditions in the brain (Wohleb and Godbout, 2013). An important task in neuroimmune studies is to determine characteristics and phenotypes of interactive immune cells. Several specialized immune cells that reside in and outside the brain are implicated (Table 1):

Microglia are long-lived, dynamic brain-resident macrophages that are derived from hematopoietic progenitors in the yolk sac and populate the brain early in development (Ginhoux et al., 2010). Microglia are distributed throughout the brain, but may have divergent roles in specific regions (Lawson et al., 1990). Recent microarray analyses support this idea showing that microglia isolated from cortex, striatum, hippocampus, and cerebellum have varied gene expression patterns (Grabert et al., 2016). In mice the primary cellular markers of microglia are CD11b, CD45^{low}, and CX_3CR1. Morphological properties of microglia are also extensively studied with immunohistology for ionized binding adaptor molecule-1 (Iba-1) (Imai and Kohsaka, 2002). Recent evidence shows that these tissue-resident macrophages develop a unique phenotype based on environmental cues derived from neurons (Gosselin et al., 2014, Kierdorf and Prinz, 2013). For instance, transforming growth factor (TGF)-β promotes a transcriptional profile that organizes the function of microglia in the brain (Butovsky et al., 2014). Indeed microglia exhibit a unique morphological phenotype in the brain with continuously surveying processes (Nimmerjahn et al., 2005). Recent studies also reveal that microglia produce soluble factors that influence neuronal function and can engulf synaptic and dendritic elements (Sierra et al., 2014, Tremblay et al., 2011).

Brain macrophages are a distinct subset of monocyte-derived immune cells that reside in the perivascular space, choroid plexus, and meninges of the brain. These specialized macrophages migrate into the brain from the blood and can reside in the perivascular space for two to three weeks. In mice the primary cellular markers for these macrophages are CD11b, CD45^{high}, and CX_3CR1; they can also express low levels of Ly6C (Prinz et al., 2011). Seminal studies showed that perivascular macrophages in the brain scan for pathogens and present antigen (Hickey and Kimura, 1988). Moreover, they play an important modulatory role in neuroimmune signaling through propagation of inflammatory signals as well as providing anti-inflammatory feedback to vascular endothelial cells (Schiltz and Sawchenko, 2003, Serrats et al., 2010).

Monocytes are a subset of hematopoietic-derived, myeloid cells that are present in the blood and spleen. Rodent studies have revealed that two distinct subsets of monocytes can be found in circulation with murine monocytes being separated into Ly6C$^-$/CX_3CR1^{high}/CCR2$^-$ and Ly6C$^+$/CX_3CR1^{low}/CCR2$^+$ groups (Geissmann et al., 2003). In functional terms, CX_3CR1^{hi} monocytes are considered "homeostatic" because they patrol blood vessels and contribute to tissue macrophage populations (Auffray et al., 2007, 2009). In contrast, CCR2$^+$ monocytes are termed "inflammatory" because they traffic to sites of inflammation and produce pro-inflammatory cytokines (Geissmann et al., 2003, Murray and Wynn, 2011). While these features can help discriminate monocyte subsets and their function, expression of chemokine receptors and markers is variable. In fact, fate mapping techniques show that peripheral monocytes may exist on a continuum as Ly6C$^+$ monocytes shift to Ly6C$^-$ monocytes over time (Yona et al., 2013). Furthermore, monocyte phenotype can be shifted based on environmental cues. For instance, infiltrating monocytes in the injured spinal cord develop an inflammatory phenotype due to pathological signals (Kigerl et al., 2009). Thus, it is necessary to use molecular and cellular analyses to determine the phenotype and function of monocyte subsets.

Vascular endothelial cells are derived from the mesoderm and undergo self-renewal throughout the life of an organism. Recent studies show that endothelial cells in the brain interact with other neural cells to form the neurovascular unit (Walchli et al., 2015). Moreover, endothelial cells that comprise blood vessels in the brain have distinctive properties, such as tight junctions that limit penetration of large molecules. Endothelial cells promote neuroimmune function through active transport of cytokines or propagation of signals *via* secondary messengers, such as prostaglandins (Quan and Banks, 2007). Some cellular markers of endothelial cells in the mouse brain are CD31 or Ly6C, and they will increase expression of cellular adhesion molecules during neuroinflammatory conditions (*i.e.*, VCAM, ICAM).

Table 1
Discerning microglia from perivascular macrophages and infiltrating peripheral monocytes. Myeloid-derived cells in the brain have varied origins and maintain residence in distinct anatomical portions of the brain. Each cell type has a determined lifespan (cell fate) and unique phenotypic markers that identify them. These characteristics help promote the function and immune responsiveness of myeloid-derived cells in the brain. Together, microglia, perivascular macrophages, and infiltrating monocytes contribute to elevated pro-inflammatory cytokines in the brain following exposure to psychosocial and environmental stressors. (cluster of differentiation 11b, CD11b; fractalkine receptor, CX3CR1; cluster of differentiation 45, CD45; colony-stimulating factor 1 receptor, CSF1R; chemokine receptor 2, CCR2; cluster of differentiation 115, CD115; blood-brain barrier, BBB).

	Microglia	Perivascular macrophages	Infiltrating monocytes
Origin	Yolk-sac myeloid cell progenitors	Hematopoietic myeloid cell progenitors	Hematopoietic myeloid cell progenitors
Residence	Brain parenchyma	Perivascular space, meninges, choroid plexus	No permanent residence in brain
Lifespan	Long-lived (years–lifetime)	Moderate (days–weeks)	Short-lived (days)
Markers (mouse)	CD11b, CD45$^{low/-}$ CX_3CR1, CSF1R, Iba-1	CD11b, CD45$^{+/high}$, CX_3CR1, CSF1R	CD11b, CD45$^{+/high}$, CCR2, Ly6C,CSF1R
Functions	Survey to maintain neuronal homeostasis and BBB integrity	Sample interstitial space for antigen and propagate systemic cytokines	Respond to pathological insults
Immune responsiveness	Propagation of cytokines and prostaglandins	Antigen presentation; Regulation of neuroimmune signaling at BBB	Rapid response to pathogens and injury; De novo production of cytokines; Debris clearance
Stress-induced alterations	Increased levels of inflammatory cytokines; De-ramified morphology	Increased presence of brain-associated macrophages; Increased levels of inflammatory cytokines	Increased number of monocytes in blood; Traffic to brain, become macrophages